

### **REMARKS**

Applicants have reviewed the Office Action mailed September 14, 2007 (the "Office Action") in connection with the instant patent application and have considered the new grounds of rejection presented therein.

Applicants thank the Examiner for withdrawing the rejections under 35 U.S.C. §§ 101, 112 (¶1), and 112 (¶2), and also for his indication that he will attend, to the extent possible, to Applicants' request for PTO records to be updated in respect of the receipt date of various filings.

#### **Statement of Substance of Interview held October 9, 2007**

Applicants' representative, the undersigned, thanks Examiner DeJong and Supervisory Examiner Moran ("the Examiners") for courtesies extended to the undersigned on the occasion of a telephonic interview (the "Interview") to discuss rejections of record, on October 9, 2007. Applicants now provide a statement of substance of the interview, as required by MPEP § 713.04.

The Interview addressed both the propriety and the underlying substance of the newly issued rejection under 35 U.S.C. § 103. Applicants' representative pointed out that the articulation of the current rejection under 35 U.S.C. § 103 as it applied to Biggin did not take into account Applicants' remarks made previously of record in the Amendment and Response filed September 27, 2006, following which a previous rejection over Biggin was overcome. The Examiners were of the view that the rejection under 35 U.S.C. § 103 was properly founded but invited Applicants to provide a rebuttal in full. Applicants' representative further attempted to solicit from the Examiners an additional understanding as to the grounds of alleged obviousness of Applicants' claims in an effort to facilitate providing a full response. Other than an indication that evidence of demonstrated success of the claimed invention would be welcomed if submitted in response to the rejection, the Examiners offered no further insights into the grounds of alleged obviousness.

**Request for Swift Conclusion of Prosecution, under MPEP § 707.02**

Accordingly, Applicants now request consideration of the instant remarks, in light of both the prosecution history of the instant application and the obligation of the Office to provide clearly articulated grounds of rejection. In particular, Applicants note the provisions of MPEP § 707.02 (“Applications Up for Third Action and 5-Year Applications”), according to which “[a]ny application that has been pending five years should be carefully studied by the supervisory patent examiner and every effort should be made to terminate its prosecution” and that “[i]n order to accomplish this result, the application is to be considered ‘special’ by the examiner.”

Applicants note that the instant application has been pending for more than 6 years, during which time it has received six (6) office actions on the merits<sup>1</sup> articulating various grounds of rejection under 35 U.S.C. §§ 101, 102, 103, 112(¶1) and 112 (¶2) (see Office Actions dated September 2nd, 2003, January 14, 2005, September 29, 2005, March 27, 2006, January 25, 2007, and September 14, 2007) all of which, except for the most recent, have to date been successfully traversed by Applicants.

Furthermore, Applicants also draw the Examiner’s attention to the principles of Full Faith and Credit as pertaining to prior examination: “Full faith and credit should be given to the search and action of a previous examiner unless there is a clear error in the previous action or knowledge of other prior art” (MPEP 716.04). The rejections of record prior to those articulated by the current examiner have been visited upon Applicants by two prior examiners, and include rejections over Biggin (as further discussed hereinbelow). If the Examiners’ previous grounds of rejection and agreement to Applicants’ grounds of traversal are now considered by the Office to have been “clear error”, then Applicants request that the Office specifically point out why that is so.

Applicants note that the reference newly cited by Examiner DeJong (van Rhree, further discussed hereinbelow) for disclosure of G-protein coupled receptors is no more than cumulative over art already of record. Furthermore, because the limitation “G-protein coupled receptors”

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<sup>1</sup> Subsequent to a first action restriction, dated November 12, 2002, that did not reach matters of substance.

had been in the claims since the application's filing date (claim 5 as originally filed; claim 36 introduced by way of Applicants' amendment, March 2, 2004), it cannot be said that Applicants' amendment on June 25, 2007 that merely introduced that term into claim 1 was sufficient to precipitate a new search and warranted new grounds of rejection.

### **Amendments to the Claims**

Claims 1, 3, and 35 – 57 and 59-64 are pending in the instant Application. With the instant amendments, Applicants amend claim 1 to recite “predicting a three-dimensional structure of a G-protein coupled receptor” thereby curing possible improper antecedent basis for “structure” in various places and reciting the claimed invention with greater particularity. Support for such an amendment can be found in the application as filed, at least at page 2, para. [0004], line 2.

Accordingly, no new matter is introduced by way of the claim amendment herein, and entry thereof is respectfully requested.

### **REJECTIONS OF THE CLAIMS**

#### **Rejections under 35 U.S.C. § 103**

The Examiner has rejected claims 1, 3, 35, 37 – 39, 41 – 46, 48, and 51 – 64, under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin *et al.*, *Biophys. Chem.* (1999) (“Biggin”), in view of van Rhee *et al.*, *Drug Devel. Res.* 37:1 – 38 (1996) (“van Rhee”). Additionally, claims 40, 49, and 50 stand rejected as allegedly obvious over Biggin, in view of van Rhee, and further in view of Mathiowetz *et al.*, *Proteins* (1994) (“Mathiowetz”), and claim 47 stands rejected as allegedly obvious over Biggin, in view of van Rhee, and further in view of Mayo *et al.*, *J. Phys. Chem.* (1990) (“Mayo”).<sup>2</sup> Applicants respectfully traverse the rejection.

The framework under which obviousness of a patent claim is judged was set forth by the U.S. Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), and is as follows. Under § 103:

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<sup>2</sup> Applicants note that since claim 58 is cancelled, the rejections only apply in sum to claims 1, 3, and 35 – 57 and 59-64. Additionally, Applicants thank the Examiners for clarifying, during the Interview, that the rejections that utilize Mathiowetz and Mayo only apply to those claims not rejected over the combination of Biggin and van Rhee alone, and not to the additional claims recited in the September 14, 2007 Office Action at pages 7 and 8.

- the scope and content of the prior art are to be determined;
- differences between the prior art and the claims at issue are to be ascertained; and
- the level of ordinary skill in the pertinent art resolved.

Based upon the answers to these factual enquiries, the obviousness or nonobviousness of the claimed subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might also be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Accordingly, and at a minimum, in order to establish obviousness of a claim, the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Furthermore, and in instances where each and every limitation of the claimed invention can be found in a combination of references, an analysis of an apparent reason to combine the known elements in the fashion claimed should be made explicit. *KSR Int'l. Co. v. Teleflex Inc.*, (04-1350, U.S. S.Ct., April 30, 2007).

The essence of the Examiner's rejection of at least claim 1 is that Biggin discloses – allegedly – Applicants' claimed method but is silent as to application of that method to G-protein coupled receptors (GPCR's). The Examiner's finding of obviousness is thus predicated on a combination of Biggin with van Rhree, which discloses a study of the effects of amino acid substitutions (mutations) on GPCR's and ligand binding thereto. This finding ignores, however, the prior prosecution history of the instant application in which other deficiencies of Biggin were established, such deficiencies meaning that Biggin fails to teach the claimed method, irrespective of its target of application. Those deficiencies (some of which reiterated again hereinbelow) are not supplied by van Rhree.

First, Applicants note that the Examiner's characterization of Biggin for the purposes of the instant rejection (under 35 U.S.C. § 103) (September 14, 2007 Office Action, at pages 4 – 6) are a verbatim recitation of the characterization of Biggin that supported the grounds of rejection under 35 U.S.C. § 102 in the Office Action dated January 14, 2005 (in paragraphs 19 – 23, 25, 27 – 29, and 31 – 33, at pages 5 – 7 of that office action). Applicants fully understand that the

same reference may be used by the Office to allege both anticipation and obviousness, but also fully expect that the rationale underlying those separate rejections be independently and properly based. To support a finding of obviousness requires showing that the references in combination do provide each and every element of Applicants' claims, as well as a rationale under which one of ordinary skill in the art would have brought those elements – if so present – into concert with one another to provide Applicants' claimed invention. If, on the other hand, one or more elements is not to be found amongst the cited references, then a rationale for obviousness must establish why one of ordinary skill in the art would have modified the references to arrive at the elements recited in Applicants' claims. Applicants do not find this line of reasoning in the current rejections of record.

Applicants have previously established that Biggin does not anticipate Applicants' claimed method for at least the reasons presented in Applicants' Amendment and Responses dated January 19, 2006, and September 27, 2006, as entered into the file history of the instant application, and incorporated herein by reference in full. Applicants summarize those reasons and present others pertinent to the current allegation of obviousness of the claims, as follows.

First, Applicants' claim 1 recites "after optimizing the helix bundle configuration, constructing one or more inter-helical loops to generate a full-atom model of the G-protein Coupled Receptor". Such a step cannot be found in the teachings of Biggin, even to the extent that Biggin applies to any membrane-bound protein (*i.e.*, not just a GPCR). This is at least because Biggin does not describe a method that involves dissecting protein structure at various levels of complexity and applying methods in succession to those various levels, as recited in the claims. Thus, Biggin does not describe optimizing a helix bundle configuration (without inter-helical loops) and, subsequently, building a full-atom model from that configuration by constructing inter-helical loops.

Applicants also respectfully submit that Biggin does not disclose separate steps of "obtaining an optimized structure for each of the two or more helices" and "assembling the optimized structures of the two or more helices into a helix bundle configuration", as recited in instant claim 1. This is again because Biggin does not present a method of modeling or

predicting a protein structure by modeling its separate units in succession. Accordingly, at least three steps recited in claim 1 are not found in Biggin. These omissions by themselves (and where not provided by secondary reference van Rhree, as further described herein) would be sufficient to overcome an allegation of obviousness over Biggin in combination with van Rhree. Nevertheless, in the interests of expediting prosecution, and securing a prompt allowance of the claims, Applicants further address why Biggin does not provide a basis upon which one of ordinary skill in the art would have contemplated deriving Applicants' claimed invention.

As set forth in Applicants' specification, Applicants' "invention provides a computational hierarchical strategy for predicting the structure of certain transmembrane proteins such as G-protein coupled receptor" (Specification at page 11, ¶ [0026]). In particular, Applicants' invention comprises at least two separately applied molecular dynamics simulations: a ('coarse-grained') simulation of a helix bundle configuration; and a ('fine-grained') optimization of a full-atom model.

By contrast, Biggin describes only single simulations on membranes (not successive simulations on various constituent parts). In particular, Biggin reviews two distinct classes of simulations, mean field simulations, and all-atom molecular dynamics simulations (both of which are applied to mechanisms of *insertion* of transmembrane helices into bilayers), but does not describe a method in which two molecular dynamics simulations are applied, successively and in concert with other intermediate steps, to different units of a protein in order to predict its three-dimensional structure. Sections 5 – 6 of Biggin describe single simulations on single helices (not helix bundles), with a particular emphasis on the surface- to inserted- transition of such helices. The mean-field simulations of Section 6 address approximations in modeling the effect of the lipid bilayer (see, *e.g.*, Biggin at p. 166, right hand col.), but also only with respect to single helices. Section 7 contrasts the all atom approach with that of mean field approaches, but the difference lies in how the bilayer is modeled (see, *e.g.*, first paragraph of section 7.1 on page 170 of Biggin) and not in the number of simulation steps carried out on a particular system.

Section 7 of Biggin describes various simulations of both individual helices, as well as helix bundles (section 7.4), but again only describes single simulations on each type of system.

Of significance is the statement on page 175 of Biggin: "MD simulations of single TM helices in an atomistic bilayer environment are feasible . . . . The future direction for such simulations will lie in their extension to biologically important problems, such as aiding the prediction of membrane protein structures." It is thus clear that Biggin acknowledges that accurate prediction of a membrane protein structure was not possible at the time of writing. Biggin does not, however, suggest Applicant's claimed method as a way to achieve such predictions. By contrast, whereas Applicants' claimed methods can predict a protein structure without prior knowledge of it, Biggin references only simulation of a system whose structure is known (bacteriorhodopsin, at, *e.g.*, pp. 177-178) as a gauge of the accuracy (albeit poor) of the single simulations described.

The numerous deficiencies of Biggin are not provided by van Rhree. Even where van Rhree describes "structure prediction" (van Rhree, pages 6 – 7), it provides a picture that is very uncertain as to accuracy and reliability of then-existing computer-based methods of predicting structure (*e.g.*, "[t]he prediction of GPCR structure from its . . . sequence is, however, less than straightforward", van Rhee, top of page 6, r.h. col.). Therefore, far from providing specific steps in a structure prediction method that might complement the disclosure of Biggin, van Rhree merely enunciates the state of the art at the time, which is that structure prediction of GPCR's was fraught with difficulty.

Accordingly, the combination of Biggin and van Rhree does not render Applicants' claims obvious because to derive Applicants' invention from such a combination it would be necessary to insert steps not explicitly taught by Biggin or the other references cited, and to rearrange disparate, unconnected, aspects of Biggin in a manner clearly not taught by Biggin or the other references cited. The Office has not provided a rationale for why or how this could be done, and Applicants believe that Biggin does not provide the requisite disclosure of teaching from which one of ordinary skill in the art would be lead to arrive at Applicants' claimed invention.

Accordingly, and in summary, for at least the foregoing reasons, the combination of Biggin and van Rhree does not provide one of ordinary skill in the art with a disclosure or teaching towards Applicants' claimed invention.

The foregoing considerations apply equally to the rejections predicated on a combination of Biggin and van Rhree, with one of Mathiowetz or Mayo, neither of which provide the deficiencies missing from Biggin and van Rhree.

Dependent claims are nonobvious under 35 U.S.C. § 103 "if the independent claims from which they depend are nonobvious." In re Fine 837 F.2d 1071; 5 USPQ.2d 1596; MPEP 2143.03. Accordingly, since claim 1 is non-obvious over Biggin in view of van Rhree, claims 3, 35, 37 – 39, 40 – 49, and 50 – 64 are similarly non-obvious. Applicants respectfully request that the rejections of record be withdrawn.

### **CONCLUSION**

In view of the foregoing remarks, Applicants respectfully submit that the subject application is in good and proper order for allowance. Withdrawal of the Examiner's rejections and early notification to this effect are earnestly solicited.

No fee is believed owed in connection with filing of this amendment and response other than the fee associated with the petition for extension of time separately authorized herewith. However, should the Commissioner determine otherwise, the Commissioner is authorized to charge any underpayment or credit any overpayment to Fish & Richardson P.C. Deposit Account No. 06-1050 (ref. No. 06618-606001) for the appropriate amount.

Respectfully submitted,

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